REMARKS

Claims 1-23 have been cancelled and Claim 24 has been amended. Thus, Claims 24-48 are presented for examination. No new matter has been added by this amendment. Applicant wishes to thank the Examiner for her examination of the pending claims.

Support for new Claims 24-48

In the Communication from the Examiner, it was requested that Applicant specifically point out support for Claims 24-48. As discussed below in detail, the specification fully supports each of the pending claims.

Claim 24:

A method of creating a "metabolic network" is supported by the specification on page 4 lines 2-4 which recites that "[t]he ability to analyze the global metabolic network and understand the robustness and sensitivity of its regulation under various growth conditions offers promise in developing novel methods of antimicrobial chemotherapy," page 5 lines 11-13 "By limiting the constraints on various fluxes and altering the environmental inputs to the metabolic network, genetic deletions may be analyzed for their affects on growth," page 10 lines 20-23 "This equation simply states that over long times, the formation fluxes of a metabolite must be balanced by the degradation fluxes. Otherwise, significant amounts of the metabolite will accumulate inside the metabolic network," page 11 lines 7-9 "Objectives for metabolic function can be chosen to explore the 'best' use of the metabolic network within a given metabolic genotype," page 12 lines 4-7 "Using linear programming, additional constraints can be placed on the value of any of the fluxes in the metabolic network.

$$\beta_j \leq v_j \leq \alpha_j$$

Equation 4," and page 15 lines 5-7 "For the analysis to determine sensitive linkages in the metabolic network of *E. coli*, the objective function utilized is the maximization of the biomass yield," as well as other locations throughout the specification.

Providing a "table of reactants and products from metabolic reactions" finds support on page 14 lines 16-18 which recites that the "genes contained within this metabolic genotype are shown in Table 1 along with the corresponding reactions they carry out." In addition, one example of a table of reactants and products is given on pages 18-39. The term "metabolic reactions" finds additional support on page 3 lines 20-21.

Selecting a nucleic acid sequence corresponding to a gene of unknown function and thereafter determining whether the sequence corresponds to a metabolic gene finds support on page 8 lines 4-5 which recites "[t]o begin the selection of this subset of genes, one can simply search through the list of functional gene assignments from state 18 to find genes involved in cellular metabolism." In addition, the specification on page 7 lines 28-30 states that "[t]his subset of genes is referred to as the metabolic genotype of a particular organism. Thus, the metabolic genotype of an organism includes most or all of the genes involved in the organism's metabolism," on page 7 lines 18-22 . The specification also states that "[a]fter the locations of the open reading frames have been determined in the genomic DNA from the target organism, well-established algorithms (i.e. the Basic Local Alignment Search Tool (BLAST) and the FAST family of programs can be used to determine the extent of similarity between a given sequence and gene/protein sequences deposited in worldwide genetic databases."

The step of adding reactants, products and stoichiometry from a gene product of the metabolic gene to the table of reactants and products is supported on page 7 lines 22-24 which recites that "[i]f a coding region from a gene in the target organism is homologous to a gene within one of the sequence databases, the open reading frame is assigned a function similar to the homologously matched gene." Then, on page 8, line 16, it is recited that "for each gene in the metabolic genotype, the substrates and products, as well as the stoichiometry of any an all reactions performed by the gene product of each gene can be determined by reference to the biochemical literature". Further, page 8, line 27 recites that "upon careful review of the biochemical literature, additional metabolic reactions can be added to the list of metabolic reactions determined from the metabolic genotype.... This would include information regarding the substrates, products, reversibility/irreversibility and stoichiometry of the reactions"

Claim 25:

With reference to this claim, "gene product" finds support on page 7 line 30 - page 8 line 3 ". The gene products produced from the set of metabolic genes in the metabolic genotype carry out all or most of the enzymatic reactions and transport reactions known to occur within the target organism as determined from the genomic sequence."

Claim 26:

This claim finds support on page 8 lines 5-8 "This would include genes involved in central metabolism, amino acid metabolism, nucleotide metabolism, fatty acid and lipid metabolism, carbohydrate assimilation, vitamin and cofactor biosynthesis, energy and redox generation, etc."

Claim 27:

This claim finds support on page 6 lines 11-15: "It should be noted that the systems and methods described herein can be implemented on any conventional host computer system, such as those based on Intel® microprocessors and running Microsoft Windows operating systems. Other systems, such as those using the UNIX or LINUX operating system and based on IBM®, DEC® or Motorola® microprocessors are also contemplated." and page 6 lines 17-19: "Software to implement the system can be written in any well-known computer language, such as Java, C, C++, Visual Basic, FORTRAN or COBOL and compiled using any well-known compatible compiler."

Claim 28:

The step of "applying constraints on said metabolic network" finds support on page 10 lines 25-27: "To determine the metabolic capabilities of a defined metabolic genotype Equation 1 is solved for the metabolic fluxes and the internal metabolic reactions, **v**, while imposing constraints on the activity of these fluxes" and page 12 lines 4-12: "Using linear programming, additional constraints can be placed on the value of any of the fluxes in the metabolic network.

$$\beta_j \leq v_j \leq \alpha_j$$

Equation 4

These constraints could be representative of a maximum allowable flux through a given reaction, possibly resulting from a limited amount of an enzyme present in which case the value for α_j would take on a finite value. These constraints could also be used to include the knowledge of the minimum flux through a certain metabolic reaction in which case the value for β_j would take on a finite value."

Claim 29:

The term "flux balance analysis" finds support on page 10 lines 8-12, page 13 lines 7-12, page 14 lines 26-28, page 16 lines 13-14 and page 17 lines 10-15, 19 & 22-23.

Claim 30:

The term "minimal media" finds support on page 15 lines 12-15 "Constraints are placed on the network to account for the availability of substrates for the growth of *E. coli*. In the initial deletion analysis, growth was simulated in an aerobic glucose minimal media culture. Therefore, the constraints are set to allow for the components included in the media to be taken up," page 17 lines 3-5 "From these studies it was shown that nearly 90% of all yeast mRNAs are present in growth on rich and minimal media, while a large number of mRNAs were shown to be differentially expressed under these two conditions."

Claim 31:

The term "optimal requirements" finds support on page 17 lines 18-19 "An important economic consideration in large-scale bioprocesses is optimal medium formulation."

Claim 32:

The term "stoichiometric matrix" finds support on page 9 lines 3-6 "All of the information obtained at states 54 and 56 regarding reactions and their stoichiometry can be represented in a matrix format typically referred to as a stoichiometric matrix. Each column in

the matrix corresponds to a given reaction or flux, and each row corresponds to the different metabolites involved in the given reaction/flux," page 9 lines 11-13 "Together all of the columns of the genome specific stoichiometric matrix represent all of the chemical conversions and cellular transport processes that are determined to be present in the organism," page 9 lines 6-7 "The resulting genome specific stoichiometric matrix is a fundamental representation of a genomically and biochemically defined genotype," page 5 lines 9-11 "Construction of a genome-specific stoichiometric matrix from genomic annotation data is illustrated along with applying flux-balance analysis to study the properties of the stoichiometric matrix, and hence the metabolic genotype of the organism," page 6 lines 2-5 "This invention relates to systems and methods for utilizing genome annotation data to construct a stoichiometric matrix representing most of all of the metabolic reactions that occur within an organism."

Claims 33 - 48:

The term "system" finds support on: page 6 lines 2-4 "This invention relates to systems and methods for utilizing genome annotation data to construct a stoichiometric matrix representing most of all of the metabolic reactions that occur within an organism" and throughout the specification.

All other terms have been shown above to have support in the specification, as discussed in detail above.

CONCLUSION

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding notice. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above.

Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be

clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

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